NHEERL Capabilities for Asbestos Toxicity Studies

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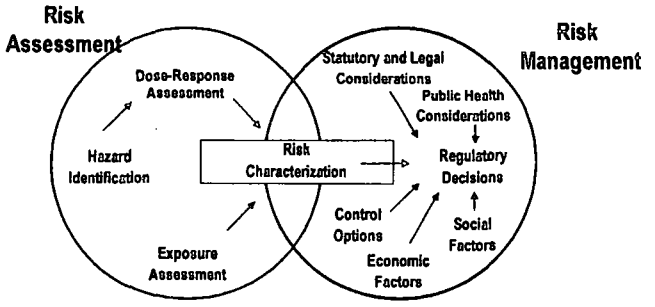
Experimental Toxicology Division
NHEERL/ORD/EPA

Superfund ORD Asbestos Meeting
Jan 17-18, 2007

Risk Assessment / Risk Management Paradigm



National Health and Environmental Effects Research Laboratory	National Center for Computational Toxicology	National Exposure Research Laboratory	National Center for Environmental Assessment	National Homeland Security Research Center	National Risk Management Research Laboratory
Research Triangle Park, NC	Research Triangle Park, NC	Research Triangle Park, NC	Washington, DC	Cincinnati, OH	Cincinnati, OH

National Center for Environmental Research
Washington, DC

RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions

NHEERL at a Glance

TOTAL WORK FORCE (as of 9/05)- 1255

- **EPA Staff - 653**
  - *scientists - 241*
  - *technical support - 265*
  - *administrative support - 91*
  - *managers - 56*
- **On-site contractors - 367**
- **Postdocs (non-feds) and graduate students - 123**
- **SEE employees- 112**

RESEARCH & DEVELOPMENT

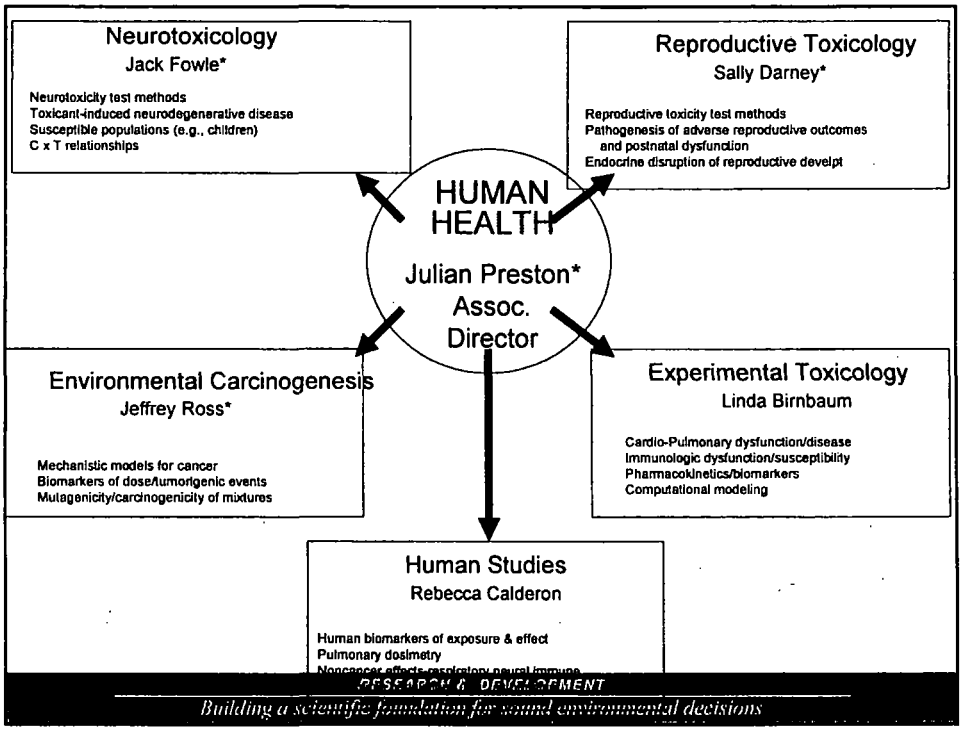
Building a scientific foundation for sound environmental decisions

NHEERL's Mission

- **Advance scientific knowledge to solve the environmental problems the Agency faces**
- **Perform human health and ecological effects *research* that provides scientific discoveries responsive to the environmental questions the Agency must address**
- **Support EPA Program Offices, Regions, and other governmental and non-governmental organizations through scientific and technical *advice and assistance* so that their operations benefit from the most up-to-date science**
- **Provide scientific *leadership* in identifying, studying, and resolving critical environmental health and ecological effects issues and in shaping the environmental health and ecological effects research agenda**

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions *...tional Strategy 2006-2008*


Neurotoxicology
Jack Fowle*
Neurotoxicity test methods
Toxicant-induced neurodegenerative disease
Susceptible populations (e.g., children)
C x T relationships
Reproductive Toxicology
Sally Darney*
Reproductive toxicity test methods
Pathogenesis of adverse reproductive outcomes and postnatal dysfunction
Endocrine disruption of reproductive develpt
HUMAN HEALTH
Julian Preston*
Assoc. Director
Environmental Carcinogenesis
Jeffrey Ross*
Mechanistic models for cancer
Biomarkers of dose/tumorigenic events
Mutagenicity/carcinogenicity of mixtures
Experimental Toxicology
Linda Birnbaum
Cardio-Pulmonary dysfunction/disease
Immunologic dysfunction/susceptibility
Pharmacokinetics/biomarkers
Computational modeling
Human Studies
Rebecca Calderon
Human biomarkers of exposure & effect
Pulmonary dosimetry
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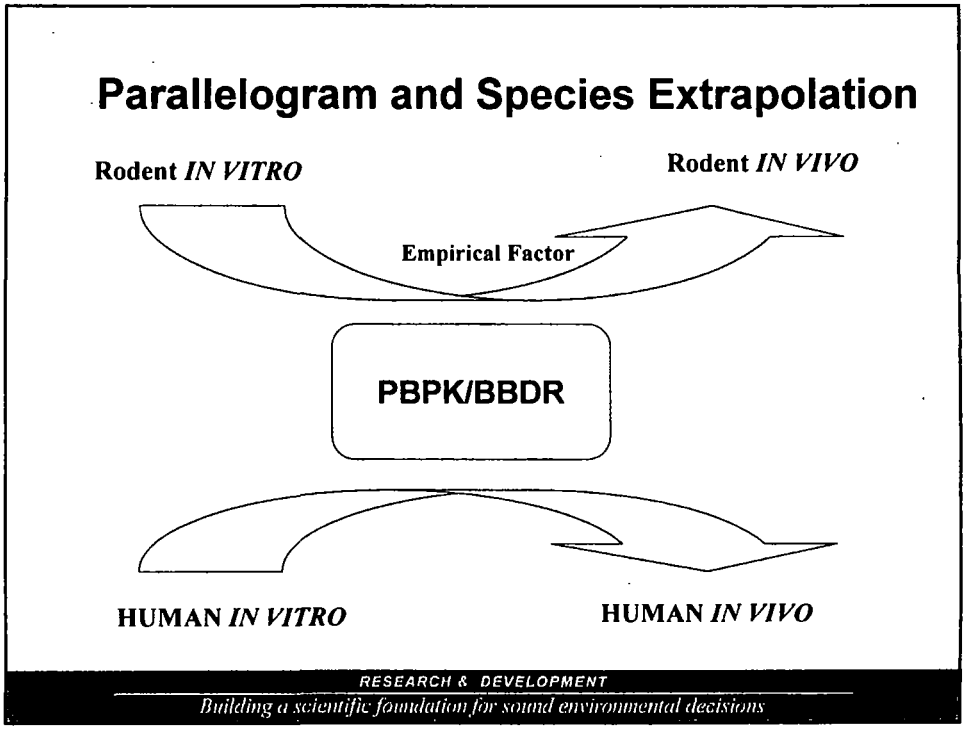
Parallelogram and Species Extrapolation
Rodent IN VITRO
Rodent IN VIVO
Empirical Factor
PBPK/BBDR
HUMAN IN VITRO
HUMAN IN VIVO
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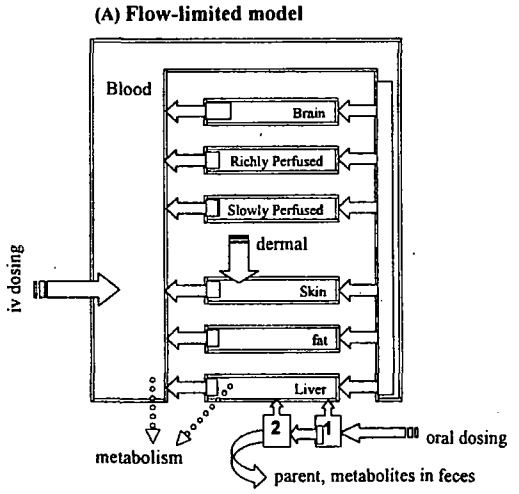
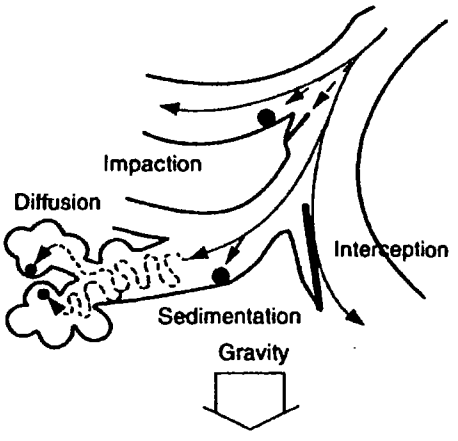
Unique Capabilities
Pharmacokinetics: PBPK Modeling



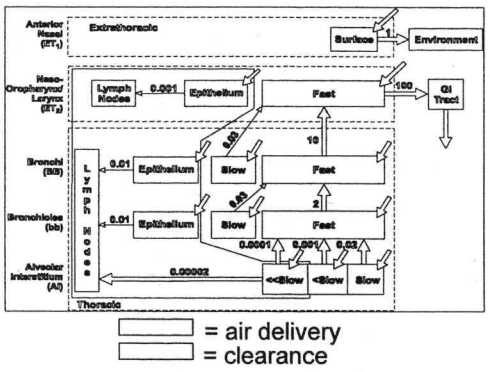
- **Uses of PBPK models**
  - ***Better incorporation of human data***
  - ***Provide estimates of target tissue concentrations***
  - ***Evaluate exposure and biomarker data***
  - ***Sets the stage for dynamic modeling***

Unique Capabilities
Inhalation Dosimetry Modeling



- **Experience with models describing particle deposition mechanisms**
- **Regional and local deposition fraction is critical determinant of toxicity**
- **Models are being extended in collaboration with CIIT and NIOSH to address fiber deposition mechanisms**

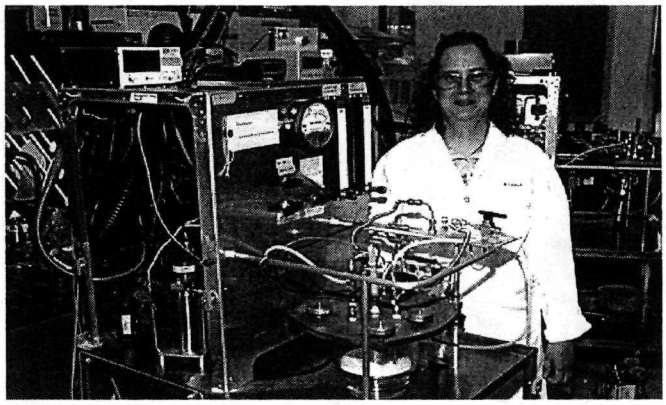
Unique Capabilities: Extending Deposition to Tissue Disposition



- Retained dose = deposition – clearance
- Clearance mechanisms
  - Dissolution
  - Physical translocation (mucociliary)
  - Phagocytosis by macrophages
  - Lymphatic drainage
- Additional determinants of tisssue response
  - Composition
  - Surface reactivity

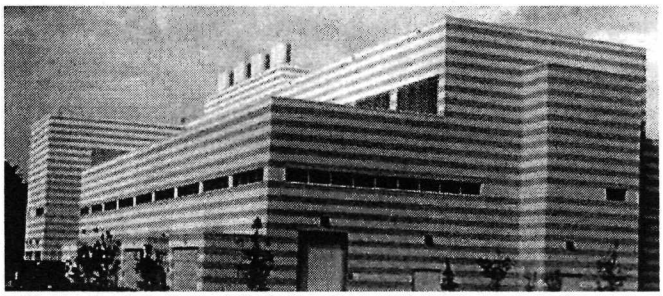
Unique Capabilities
Pharmacokinetics: Gas Uptake Facility

Our *Core Gas Uptake Facility* provides unique opportunities to solve complex problems associated with air and water pollutants.



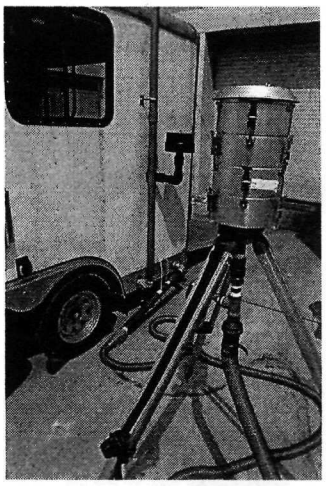
Unique Capabilities
Inhalation Toxicology
Animal Inhalation Exposure Systems for Air Pollution Research

- Gases – Vapors – Particles - Microbials
- Complex Mixtures - Combustion Atmospheres

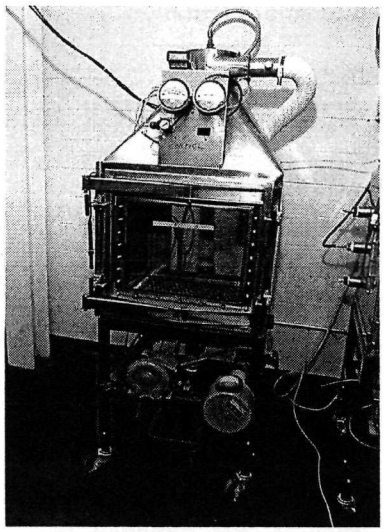


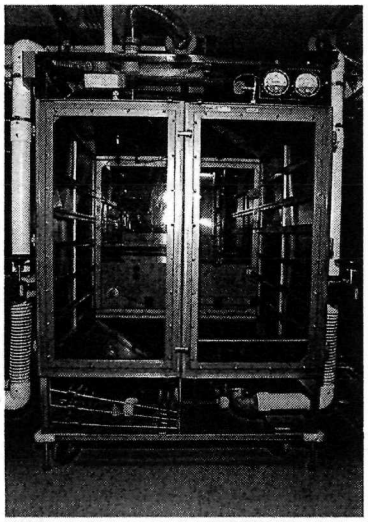
EPA's High Bay facility in Research Triangle Park, NC.

Unique Capabilities
Inhalation Toxicology
Mobile Samplers



Inhalation Toxicology: *Unique Capabilities*
Inhalation Exposure Chambers



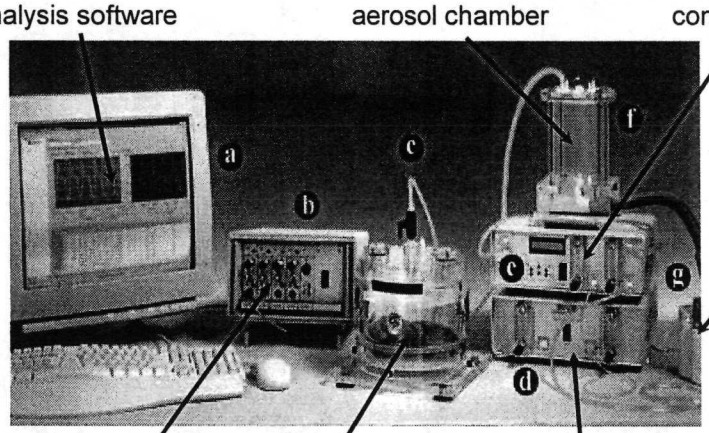


Unique Capabilities
Cardiopulmonary Toxicology

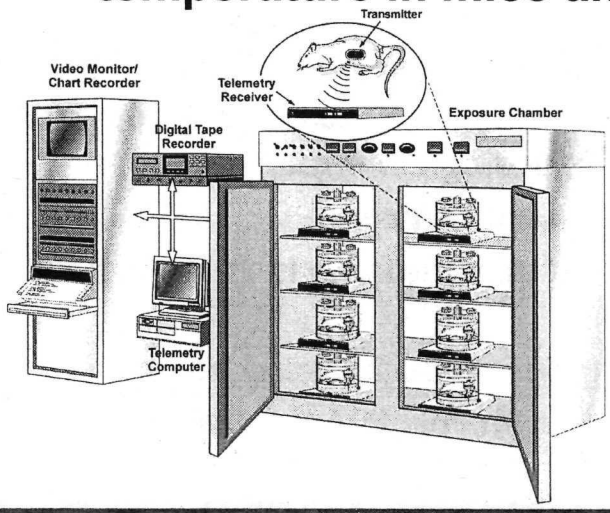
- **Automated Research Biochemistry Analyzer**
  - ***Measures over 70 enzymes and endogenous chemicals of biological importance***
    - ***>65,000 samples/year***
- **Measurement of Antioxidants in Biological Tissues**
  - ***Protection against pollutant exposure***
    - ***Glutathione, Ascorbic Acid, Uric Acid, α-Tocopherol***

Pulmonary Physiology in Small Animals

Assessment of Airway Obstruction in Unanesthetized Unrestrained Rodents (Buxco)



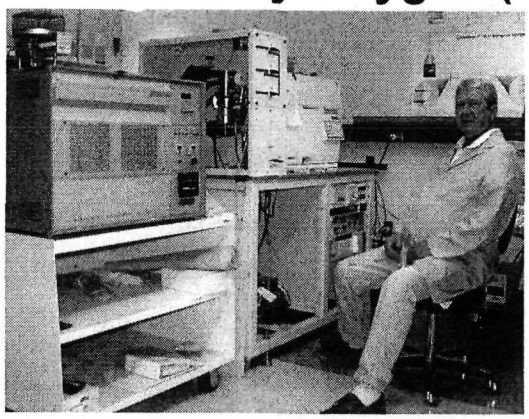
Radiotelemetry measurement of heart rate, blood pressure and body temperature in mice and rats.



Toxic effects of pollutants on the body are sensitively measured by and transmitted by transmitters implanted surgically.

Technique developed at EPA.

Measurement of Low-level Oxidation of Biological Tissues using Heavy Oxygen (Oxygen-18).

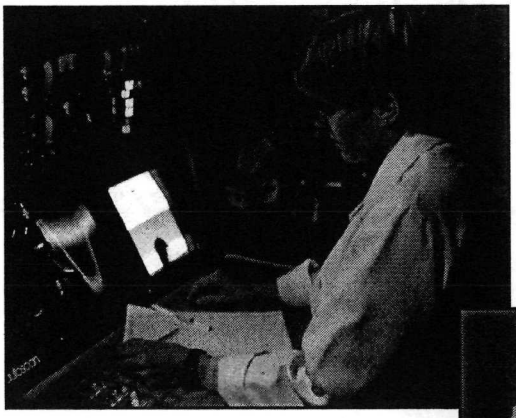


A geological technique for measuring heavy oxygen by mass spectrometry has been modified and applied to biological tissues to measure the effects of oxidant pollutants and the aging process.

Unique Capabilities - *Immunotoxicology*

- Test Methods for Adult and Developmental Immuntoxicology
- Infectivity Models
  - ***Bacterial, Viral, Parasitic***
  - ***Pulmonary, GI, Dermal***
- Cutaneous Hypersensitivity
- Asthma
  - ***Indoor Molds***
  - ***Outdoor Air Pollutants***
  - ***Low Molecular Weight Chemicals***

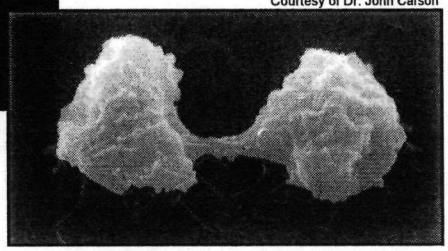
Laboratory Studies



Electron Microscopy

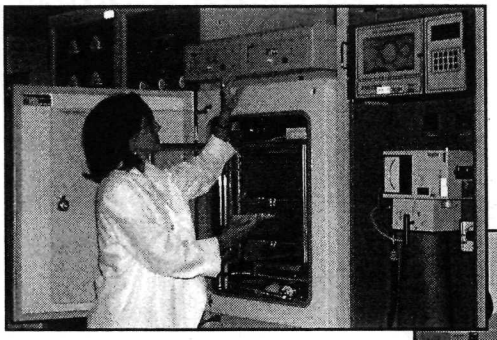
Confocal Microscope

Courtesy of Dr. John Carson

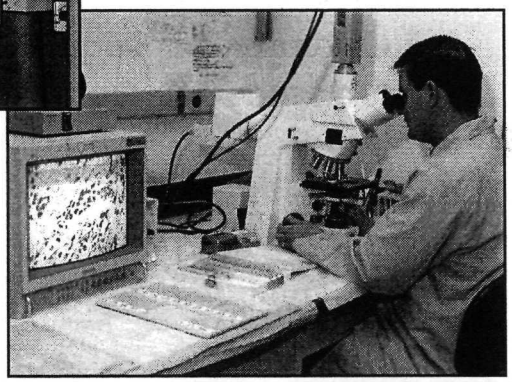


Mitotic Cell Division of an A549 Cell

Laboratory Studies



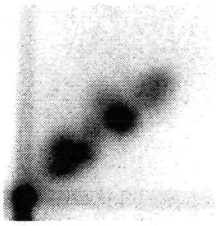
***In vitro* exposure chamber**

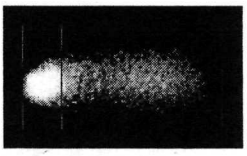


Computer-assisted image analysis

Genotoxicity Assessment Capabilities

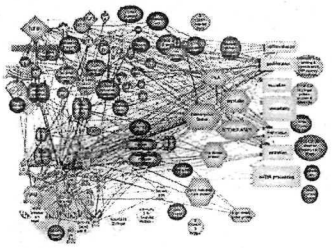
- Bacterial and mammalian cell mutagenicity assessment
- *In vivo* mammalian mutagenicity assessment
- DNA damage analyses
  - Adduct analysis
  - Single-cell gel electrophoresis
- Chromosomal alterations

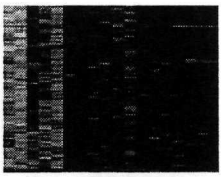


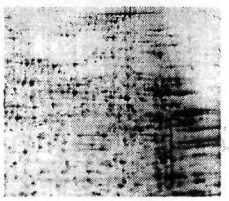


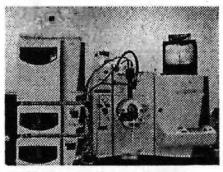
Genomics and Proteomics

- Altered gene expression
- Activation/repression of pathways
- Alterations in protein levels
- Alterations in post-translational modifications of proteins
- Analysis of protein damage

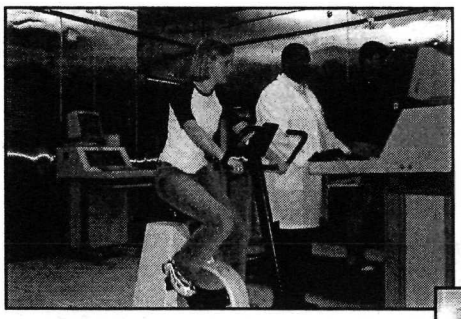




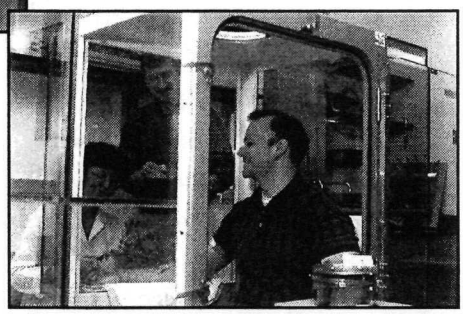




Clinical Studies



Exercise equipment used during controlled exposure studies.



Pharmacokinetic chamber

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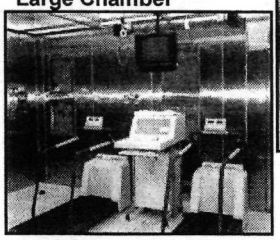
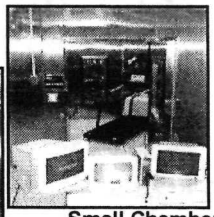
National Facility - Chambers

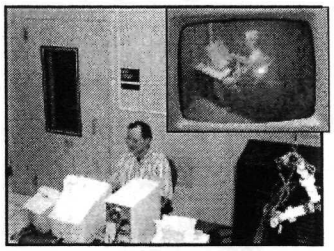
Large Chamber



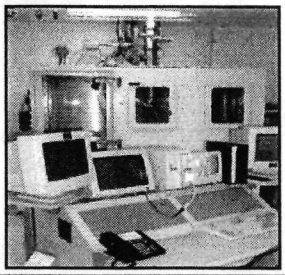


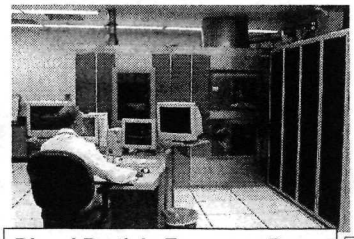
Small Chamber

Audiometric Chambers

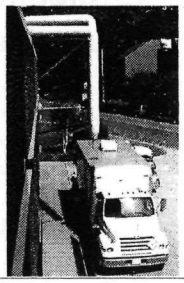


Concentrated-PM Air Chamber





Diesel Particle Exposure Room



Diesel Particle Generator

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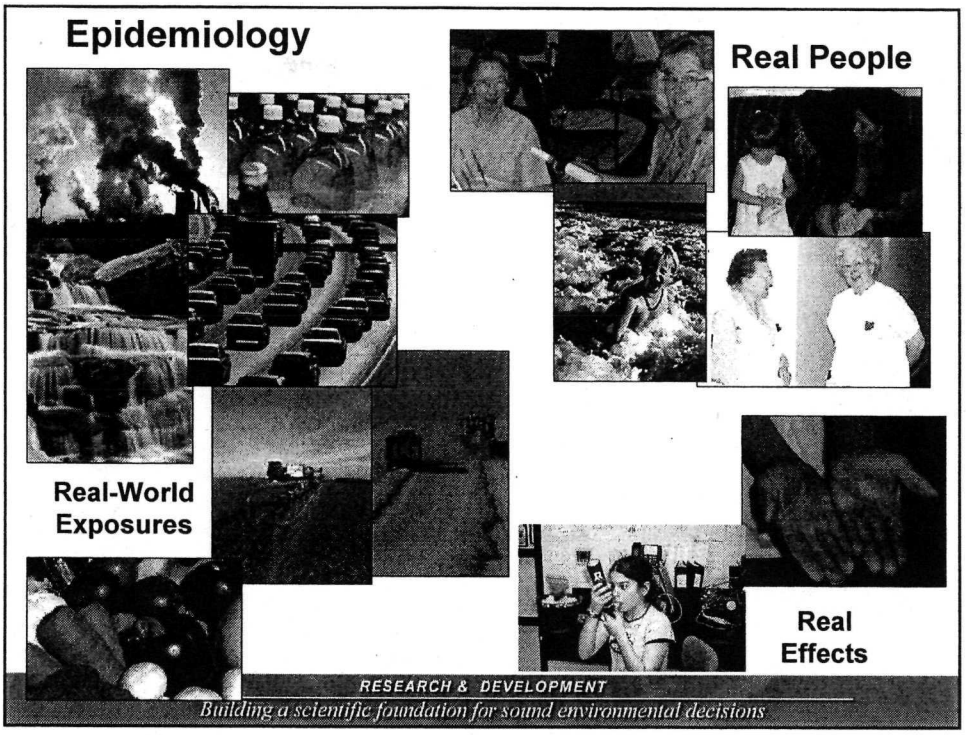

NHEERL is Ready to…

- Conduct Asbestos Toxicity Research
- Provide Technical Advice and Assistance

THANK YOU!

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